Behavioral/Systems/Cognitive

# Scaling of Movement Is Related to Pallidal γ Oscillations in Patients with Dystonia

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**Neuronal synchronization in the gamma (γ) band is considered important for information processing through functional integration of neuronal assemblies across different brain areas. Movement-related γ synchronization occurs in the human basal ganglia where it is centered at ~70 Hz and more pronounced contralateral to the moved hand. However, its functional significance in motor performance is not yet well understood. Here, we assessed whether event-related γ synchronization (ERS) recorded from the globus pallidus internus in patients undergoing deep brain stimulation for medically intractable primary focal and segmental dystonia might code specific motor parameters. Pallidal local field potentials were recorded in 22 patients during performance of a choice-reaction-time task. Movement amplitude of the forearm pronation-supination movements was parametrically modulated with an angular degree of 30°, 60°, and 90°. Only patients with limbs not affected by dystonia were tested. A broad contralateral γ band (35–105 Hz) ERS occurred at movement onset with a maximum reached at peak velocity of the movement. The pallidal oscillatory γ activity correlated with movement parameters: the larger and faster the movement, the stronger was the synchronization in the γ band. In contrast, the event-related decrease in beta band activity was similar for all movements. Gamma band activity did not change with movement direction and did not occur during passive movements. The stepwise increase of γ activity with movement size and velocity suggests a role of neuronal synchronization in this frequency range in basal ganglia control of the scaling of ongoing movements.**

## Introduction

Neuronal synchronization in the gamma (γ) frequency range (> 30 Hz) has been found in different brain areas and has been related to specific functions, such as vision, somatosensory processing, memory, and motor preparation (Bauer et al., 2006; Engel et al., 2001; Jensen et al., 2007; Schoffelen et al., 2005; Buzsáki, 2006). Synchronization of γ band activity is considered as an efficient temporal code for implementing complex forms of information processing afforded by neuronal coherence (Varela et al., 2001). Movement-related induced γ band activity can be recorded in the electrocorticogram from the motor cortex of patients with epilepsy contralateral to the side of the movement (Crone et al., 1998; Pfurtscheller et al., 2003) and has been localized to the contralateral human motor cortex in healthy subjects using noninvasive magnetencephalography (MEG) (Cheyne et al., 2008). While the functional role of γ synchronization in cortical areas is increasingly appreciated, γ band activity in the human basal ganglia (BG) has only recently been found in patients undergoing deep brain stimulation (DBS) for severe movement disorders.

In patients with Parkinson's disease (PD), increased 60–80 Hz activity has been considered prokinetic (Brown, 2003) since it occurs in the subthalamic nucleus (STN) and globus pallidus internus (GPi) at rest after intake of dopaminergic medication in parallel with improvement of motor symptoms (Brown et al., 2001; Cassidy et al., 2002; Silberstein et al., 2003) and was associated with dyskinesia (Fogelson et al., 2005). Movement-related γ synchronization has been found predominantly contralateral to the moved side in various basal ganglia nuclei and the thalamus in patients with different pathologies (Kempf et al., 2007; Androulidakis et al., 2007; Alegre et al., 2005; Brücke et al., 2008b; Liu et al., 2008; Lalo et al., 2008; Kempf et al., 2009), suggesting its general role in information processing in the BG.

However, there has been little work addressing how induced γ band activity in the human BG relates to specific parameters of motor processing during preparation or performance of a movement. The precise function of the basal ganglia in motor control is still debated (for review, see Turner and Desmurget, 2010). One influential theory hypothesizes that BG play an important role in scaling of movements, and local inactivation of the GPi reduces

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movement amplitude, speed, and acceleration in monkeys (Horak and Anderson, 1984; Desmurget and Turner, 2008; Mink and Thach, 1991c). Similarly, pallidal DBS may induce slowness of movement in patients with dystonia (Ostrem et al., 2007; Berman et al., 2009; Blahak et al., 2011).

The aim of the present study was to explore different movement parameters such as amplitude, speed, and movement direction in relation to γ band synchronization in the human BG. Since we set out to examine movement parameters in a state "as normal as possible," local field potential activity was recorded from the GPi in patients undergoing DBS for cervical or segmental dystonia with preserved normal hand motor function. We found a movement-related increase in pallidal synchronized γ band activity that was related to movement amplitude and velocity, regardless of the direction of movement.

## Materials and Methods

*Patients and surgery.* Local field potentials (LFP) from the GPi were recorded from 22 patients suffering from primary dystonia during performance of a choice-reaction-time task. Clinical details are given in Table 1. Nineteen patients were diagnosed with a focal cervical dystonia, three patients had a segmental dystonia. Eleven patients were male and 11 female. Patients took part with informed consent, the permission of the local ethics committee of the Charité, University Medicine Berlin and the Hannover Medical School and in accordance with the standards set by the Declaration of Helsinki. They underwent simultaneous bilateral implantation of DBS electrodes in the GPi. The surgical procedure has been described previously (Kupsch et al., 2006; Reese et al., 2011; Brücke et al., 2008b). The DBS electrode used was model 3389 (Medtronic Neurological Division) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a contact-to-contact separation of 0.5 mm. Target coordinates were based on direct visualization of the GPi in the individual stereotactic $T_2$-weighted MRI. The intended coordinates at the tip of electrode 0 were 17.4–22 mm lateral from the midline, 2–4 mm in front of the midcommissural point, and 2–4 mm below the midcommissural point as determined by MRI adjusted to the individual patient's anatomy. Correct placement of the DBS electrode was confirmed by intraoperative microelectrode recordings and direct macrostimulation in all patients. Moreover, localization of DBS electrodes was verified by postoperative MRI (Berlin) or stereotactic CT (Hannover) imaging using automated normalization and contact localization in standard Montreal Neurological Institute (MNI) stereotactic space coordinates [methods are described in more detail in the study by Schönecker et al. (2009)] in all patients (except for case 16 and 22 where image quality of postoperative CT was not sufficient). Evaluation of clinical efficacy of chronic DBS on motor symptoms revealed an overall mean improvement of 46.5% [using TWSTRS (Toronto Western spasmodic torticollis rating scale, case 1–8 and 10–22) and BFMDRS (Burke–Fahn–Marsden dystonia rating scale, case 9) at least 3 months after DBS surgery], which further supported correct placement of DBS electrodes in our patients.

*Recordings.* LFP recordings were made on average at 3 ± 1 (range 1–4) d postoperatively before chronic stimulation was commenced. GPi LFPs were recorded bipolarly from the four adjacent contacts of each DBS electrode (contact pairs 01, 12, 23). The bipolar setup was used to ensure a local origin of signals and minimizes the possibility of cortical activity picked up by the electrodes (Kühn et al., 2004). Signals were amplified (×50,000) and filtered at 1–250 Hz using a custom-made, high-impedance amplifier (which had as its front end input stage the INA128 instrumentation amplifier, Texas Instruments Incorporated 12500 TI Boulevard) or a Digitimer D360 amplifier with bandpass filter set at 0.5–500 Hz and recorded through a 1401 A-D converter (Cambridge Electronic Design) onto a computer using Spike2 software (Cambridge Electronic Design; cases 3–5, 8–11, 14–16, 18–22). Signals were sampled at 1 kHz and monitored online. In cases 1, 2, 6, 7, 12, 13, and 17 a different amplifier (Biopotential Analyzer Diana) was used with a sampling rate of 1.5 kHz. EMG activity was recorded from upper limb muscles during arm movements using Ag–AgCl surface electrodes, filtered at 10–250 Hz and amplified (×1000) and recorded as described above. EEG recordings were obviated by surgical wound dressing in our patients.

*Paradigm.* LFPs were recorded while patients engaged in a choice-reaction time task where forearm pronation movements with three different amplitudes had to be performed (see schematic of paradigm, Fig. 1*A*). Patients were seated comfortably in a chair and held a rotatable light handle with one hand. Rotation movements were sensed using a potentiometer and recorded via a 1401 A-D converter onto a computer using Spike 2 software. One of three possible cues appeared in randomized order on a laptop screen for 1 s and with intertrial periods of 4–6 s. Cues indicated the size of the required forearm pronation movements to reach the target position (Fig. 1). The patients were instructed to perform the movement as quickly and accurately as possible. The aim was to reach the indicated target positions with a swift movement of the handle (pronation) and to rotate the handle back to the start position (supination) without delay after reaching the target position. The arm movements differed in the maximal angular amplitude that was necessary to reach the target position: small (S, 30°), medium (M, 60°), and large (L, 90°) amplitude arm movements. The position of the handle was shown online on the laptop screen as a red dot in relation to the start and target positions in 13 patients (cases 10–22, 21 sides). Patients 1–9 had no such visual feedback. Patients performed the experiment separately with the right and left arm. Eight of the 22 patients performed the task with only one arm due to time constraints or because prominent dystonic laterocollis obviated maintenance of a constant position with which to view the laptop screen while holding the handle of the device. A total of 36 sides were tested. Importantly, patients did not show dystonic features of the hand as judged by clinical examination. The analysis of movement-related changes in neuronal activity was limited to the initial phase of the movement, i.e., the pronation movement to reach the target position. In addition to the parametric three step increase of movement amplitude, we investigated the relation between γ synchronization and movement amplitude/speed on a single trial level with freely chosen movement size within a range from 1° to 90° in a single subject (patient 2, left hand movements). Movements were externally paced but no target amplitude was given ($n = 62$ trials).

To explore whether movement-related γ band synchronization was sensitive to movement direction, four patients repeated the initial task (with initial pronation movements) with reverse movement direction starting with supination movements (patients 4, 7, 8, and 13; $n = 5$ sides). The mean γ band activity during the initial movement phase (0–300 ms after movement onset) was compared between movements with opposing directions.

To ensure that pallidal γ synchronization was related to the active movement rather than induced by proprioceptive afferents during arm movements, we performed passive movements in a subgroup of patients (patients 10–13, $n = 6$ sides). Here, patients held the handle of the device but tried to keep their arm as relaxed as possible while the handle was moved by the investigator with similar velocity as in the active movement trials. Trials were visually inspected and periods of increased EMG activity during the passive pronation movements were excluded from further analysis.

*Analysis.* Files with a higher sampling rate were resampled to a common sampling rate of 1 kHz. LFP traces were visually checked for artifacts and trials with a reaction time >1 s or where the patient executed the wrong movement were rejected, leaving an average of 38 ± 3 (S, range 21–64), 39 ± 3 (M, range 26–68), and 38 ± 3 (L, range 21–68) trials per movement condition per side for further analysis (no significant difference between movement conditions).

Movement-related changes in neuronal synchronization were calculated in trials of 6 s duration and expressed as percentage change from baseline activity (calculated from −2 to −1 s before movement onset) separately for each movement amplitude. To better separate LFP oscillatory changes related to movement amplitude or speed, LFP traces were aligned to three different time points: (1) movement onset (MO), (2) maximum velocity per trial (maxV), and (3) the time point of reaching the target position, i.e., maximum amplitude (maxA). Spectra were estimated using the sliding window discrete Fourier transform in Spike2 with a window size of 512 data points (centered on time 0 assigned

**Table 1. Patient details**

| Patient ID | Surgical center | Age/ Gender | Disease duration in years | Disease/Affected body part | Clinical scores preOP (TWSTRS severity subscore) | Clinical scores postOP (TWSTRS severity subscore) | Medication | Selected contact | Stimulation settings |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Hannover | 45/M | 8 | Cervical dystonia | 20 | 8 | Trihexiphenidyl 8 mg/d | R12 L12 | R: 1−,2+; 210 μs, 130 Hz, 5.2 V<br>L: 1−, 2+; 210 μs, 130 Hz, 5.2 V |
| 2 | Hannover | 64/M | 4 | Segmental dystonia (neck, mouth) | 21 | 8 | Lorazepam 2 mg/d | R12 L01 | R: 1−,2+; 210 μs, 130 Hz, 3.2 V<br>L: 1−, 2+; 210 μs, 130 Hz, 3.32 V |
| 3 | Berlin | 57/F | 8 | Cervical dystonia | 23 | 10 | Clonazepam 2 mg/d | R12 | R: 1−,2− 90 μs, 180 Hz, 2.2 V<br>L: 1−,2−; 90 μs, 180 Hz, 3 V |
| 4 | Berlin | 50/F | 9 | Cervical dystonia | 28 | 4 | None | R23 L01 | R: 2−, 3−; 90 μs, 130 Hz, 3,3 V<br>L: 2−, 3−; 90 μs, 130 Hz, 3,5 V |
| 5 | Berlin | 56/F | 9 | Cervical dystonia | 16 | 17 | Trihexyphenidyl 14 mg/d, Mirtazapine 15 mg/d, Tetrazepam 200 mg/d | R01 L12 | OFF/ no treatment response |
| 6 | Hannover | 50/F | 8 | Cervical dystonia | 23 | 10 | Clonazepam 2 mg/d | R23 | R: 1−,2+; 210 μs, 130 Hz, 3,8 Volt<br>L: 1−, 2+; 210 μs, 130 Hz, 3.8 Volt |
| 7 | Berlin | 56/F | 4 | Cervical dystonia | 26 | 10 | Trihexyphenidyl 15 mg/d | R01 L12 | R: 1−, 90 μs, 180 Hz, 3.7 V<br>L: 2−; 90 μs, 180 Hz, 3.7 V |
| 8 | Berlin | 41/M | 9 | Cervical dystonia | 23 | 11 | None | L12 | R: 2−, 120 μs, 130 Hz, 4.5 V<br>L: 2−; 120 μs, 130 Hz, 3.3 V |
| 9 | Berlin | 57/F | 2 | Focal dystonia (mouth) | 4/40[a]<br>12/120[b] | 3/40[a]<br>10/120[b] | None | R01 L23 | R: 1−, 2−, 90 μs, 130 Hz, 2.1 V<br>L: 1−, 2−; 90 μs, 130 Hz, 2.2 V |
| 10 | Berlin | 51/M | 15 | Cervical dystonia | 23 | 18 | Lithium 900 mg/d, Escitalopram 10 mg/d | R12 L12 | R: 3−, 90 μs, 130 Hz, 6 V<br>L: 3−; 90 μs, 130 Hz, 6 V |
| 11 | Hannover | 38/M | 23 | Segmentale dystonia | 25 | 12 | None | L12 | R: 1−,2+; 210 μs, 130 Hz, 2.4 V<br>L: 1−, 2+; 210 μs, 130 Hz, 1.8 V |
| 12 | Hannover | 49/M | 12 | Cervical dystonia | 15 | 8 | Clonazepam 2 mg/d | L01 | R: 1−,2+; 210 μs, 130 Hz, 3,2 Volt<br>L: 1−, 2+; 210 μs, 130 Hz, 3.2 Volt |
| 13 | Hannover | 46/M | 5 | Cervical dystonia | 24 | 16 | Citalopram 20 mg/d | R01 L12 | R: 1−, 2+; 120 μs, 130 Hz, 5.3 V<br>L: 1−, 2+; 120 μs, 130 Hz, 5.3 V |
| 14 | Berlin | 57/F | 7 | Segmental dystonia (neck, mouth) | 23 | 10 | None | L01 | R: 0−,1−; 90 μs, 180 Hz, 2.6 V<br>L: 0−,1−; 90 μs, 180 Hz, 2.6 V |
| 15 | Berlin | 55/M | 8 | Cervical dystonia | 25 | 12 | None | R23 L23 | R: 1−,2−; 90 μs, 135 Hz, 2.1 V<br>L: 1−,2−; 90 μs, 130 Hz, 2.1 V |
| 16 | Hannover | 57/M | 21 | Cervical dystonia | 27 | 20 | Clonazepam 2 x 1 mg | R23 L01 | R: 1−,2+; 180 μs, 130 Hz, 3.5 V<br>L: 1−, 2+; 180 μs, 130 Hz, 3.6 V |
| 17 | Hannover | 66/M | 17 | Cervical dystonia | 19 | 8 | Lorazepam 2 mg/d<br>Baclofen 100 mg/d | L12 | R:1−,2+; 210 μs, 130 Hz, 1.7 V<br>L: 1−, 2+; 210 μs, 130 Hz, 2 V |
| 18 | Berlin | 53/F | 3 | Cervical dystonia | 23 | 9 | Telmisartan 40 mg/d, Hydrochlorothiazid 12.5 mg/d | L23 | R: 1−; 90 μs, 140 Hz, 3 V<br>L: 2−; 90 μs, 140 Hz, 3.5 V |
| 19 | Berlin | 43/F | 8 | Cervical dystonia | 18 | 10 | Tetrazepam 50 mg/d | R12 L01 | R: 1−; 60 μs, 130 Hz, 2.8 V<br>L: 1−; 60 μs, 130 Hz, 2.8 V |
| 20 | Berlin | 33/M | 2 | Cervical dystonia | 23 | 14 | None | R01 L12 | R:2−,3−; 90 μs, 130 Hz, 2.3Volt<br>L:2−, 3−; 90 μs, 130 Hz, 1.5 Volt |
| 21 | Berlin | 49/F | 7 | Cervical dystonia | 20 | 8 | None | R12 L12 | R: 2−; 90 μs, 130 Hz, 1.7 V<br>L: 2−; 90 μs, 130 Hz, 3.1 V |
| 22 | Hannover | 67/F | 5 | Cervical dystonia | 14 | 5 | L−Thyroxin 75 μg/d | R12 L12 | R: 1−,2+; 210 μs, 130 Hz, 3 V<br>L: 1−, 2+; 210 μs, 130 Hz, 3 V |
| Mean (±SD) | | 52 (±8)<br>11 F, 11 M | 8.8 (±5.6) | | 21.9 (±3.8) | 10.9 (±4.1) | | | |

M, Male; F, female; R, right; L, left.

[a]AIMS (Abnormal involuntary movement scale).

[b]Burke–Fahn–Marsden dystonia rating scale, movement subscale.

time = 0) and shifted in 100 ms steps across epochs. A Hanning window was applied to attenuate edge effects. The frequency resolution of spectra was 1.95 Hz. LFPs were analyzed over frequencies between 1 and 200 Hz. Time-frequency plots were calculated showing median percentage power changes relative to baseline for pallidal LFPs averaged over all contact pairs per electrode, separately for the contralateral and ipsilateral side.

According to the main oscillatory changes seen in the grand average from all patients and in line with the results of previous studies (Androulidakis et al., 2007; Brücke et al., 2008a,b), we determined specific time periods and frequency bands of interest (β-band: 20–30 Hz from −300 ms to 300 ms around MO; γ-band: 60–80 Hz from MO to 300 ms after MO) for the main analysis. Since there were no task-specific changes in oscillatory activity in pallidal recordings ipsilateral to the moved side, all further analysis was limited to the contralateral GPi. Furthermore, the contact pair that displayed the largest power changes compared with baseline activity in the region of interest averaged over the three movement conditions was selected for all further analysis. Contact evaluation

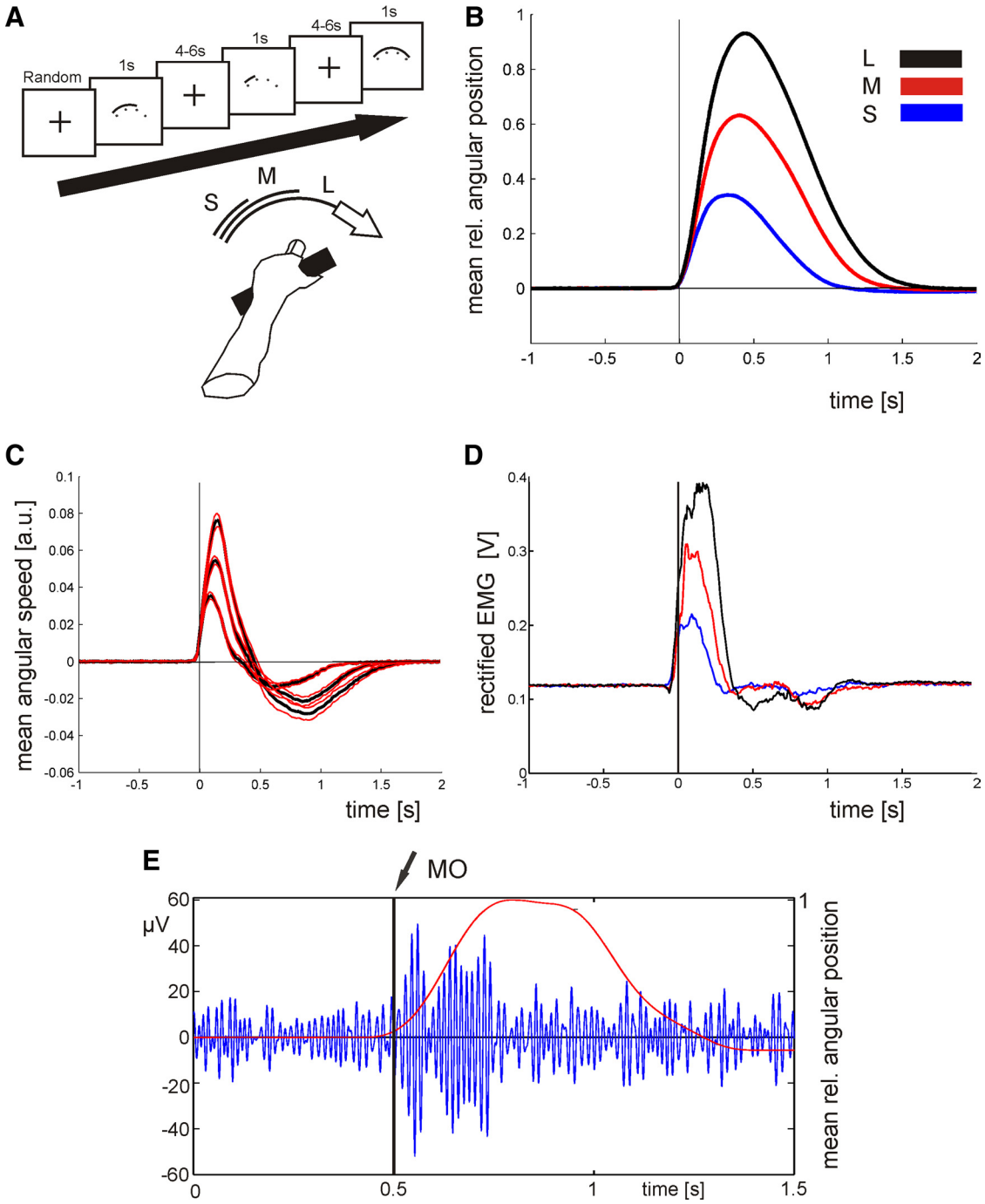


**Figure 1.** ***A***, Schematic illustration of the paradigm. ***B***, Mean relative angular movement positions averaged across sides (small amplitude movement in dark blue, medium amplitude movements in red, and large amplitude movements in black). ***C***, Mean angular speed averaged across sides separately for the three conditions (mean ± SE). ***D***, Mean rectified EMG activity from the forearm of patient 4. ***E***, Trace of 55–90 Hz filtered LFP during a movement with large amplitude (blue) and angular movement position (red) from patient 7.

revealed that at least one of the contacts from each bipolar recording used for the main analysis lay within GPi on postoperative imaging (not known for case 16 and 22 where postoperative imaging data were not available; Fig. 2). In case 2, single trial analysis was performed on filtered γ band activity (60–80 Hz) and movement speed and amplitude of each trial were correlated with the γ band response 300 ms around MO, maxA, and maxV.

To define distinct peaks in the power spectrum, we calculated Fast Fourier Transform (FFT)-based power spectra using 1 Hz frequency resolution on one rest-recording data segment (55–200 s) in each patient.

*Statistics.* Since movement related oscillatory activity was not normally distributed between patients in all time-frequency coordinates as assessed by the Kolmogorov–Smirnov test (using the command "kstest" from the Matlab statistics toolbox, The MathWorks), movement-related power changes across all patients were analyzed by means of the non-parametric Wilcoxon's signed rank test (command "signrank," statistics toolbox) and Friedman's test of related samples (command "friedman"). In each time-frequency bin of the median time-frequency plot we tested whether changes in contralateral and ipsilateral GPi during arm movements were different from baseline, and compared the time-frequency bins between the three movement conditions and between ipsilateral and contralateral sides. This provided matrices with each bin represented by its respective $p$ value. To correct for multiple comparisons in time-frequency analysis, the false discovery rate (FDR) procedure was used

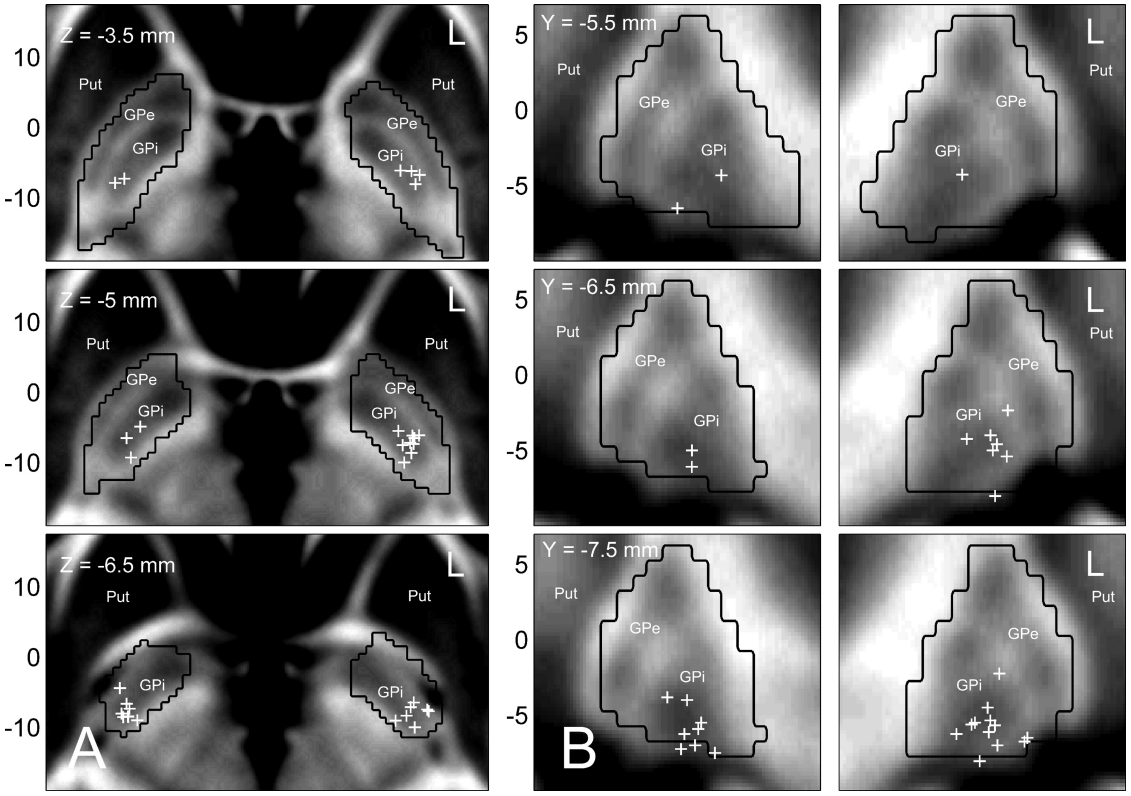


**Figure 2.** Localizations of contact pairs of the DBS electrodes in standard MNI stereotactic space coordinates (dimensions in mm: X: mediolateral, Y: anteroposterior, Z: dorsoventral direction). ***A***, ***B***, Localizations of the center (+) of the bipolar contact pairs selected for LFP analysis are depicted (white crosses; L, left side) on corresponding horizontal slices (***A***) and coronal slices (***B***) of the MNI standard brain template with the structures: putamen (put), globus pallidum ext. (gpe), globus pallidum int. (gpi). In relation to the center point of the anterior commissure, the horizontal level $z = -3.5$ mm is located ~0.8 mm more dorsal and the level $z = -5$ mm is located 0.7 mm more ventral. Mean nuclear boundaries of the globus pallidus are outlined (black) based on the Harvard–Oxford subcortical probabilistic structural atlas ($n = 20$ patients). Note that the actual contacts are located up to 1.75 mm more dorsal (proximal contact) and more ventral (distal contact) with respect to the displayed center of the contact pairs.

and the thresholds corresponding to the $\alpha$ level of $p < 0.01$ were calculated (Benjamini and Hochberg, 1995).

For the subsequent analysis, looking at the effects of movement parameters on neuronal activity in selected frequency bands and time-windows (60–80 Hz: 0–300 ms after MO; 20–30 Hz: −300 to 300 ms after MO), changes from baseline power were normally distributed according to Kolmogorov–Smirnov test and therefore assessed by repeated-measures ANOVA (PASWStatistics 18, SPSS) with factor MOVEMENT CONDITION (3 levels: S, M, and L) tested separately for power changes related to MO, maxV, and maxA. Subgroup analysis controlling for modifications in online feedback of the movement was performed using the between-subject factor FEEDBACK. *Post hoc* Student's *t* tests were performed to determine relevant differences in event-related power changes, and results were corrected for multiple comparisons using Bonferroni corrections. All behavioral parameters (movement speed, amplitude, and reaction time) were assessed using repeated-measures ANOVA with the factors MOVEMENT CONDITION.

The mean relative change in movement velocity between conditions was correlated with the mean relative modulation in γ band activity across subjects (Pearson's correlation). Additionally, single-trial analysis was performed in a single subject to evaluate the correlation between the average root-mean square amplitude of the 60–80 Hz filtered LFP traces from each trial averaged 300 ms around MO, maxV, and maxA and the movement speed of the corresponding trial using Pearson's correlation. All results are reported as mean ±SEM, unless stated otherwise.

## Results

### Behavioral data

Patients performed the task with a mean reaction time of 0.49 ± 0.03 s. The three conditions differed in amplitude and angular velocity of the arm movements (Fig. 1*B–D*; repeated-measures ANOVA $F_{(1.7)} = 4620$; $p < 0.001$, $F_{(1.2)} = 230.6$; $p < 0.001$, Huyhn–Feldt corrected, respectively). This was the same whether or not visual feedback of the ongoing movement was given online. The target position was reached at different time points with respect to movement amplitude (S: 0.40 ± 0.02 s; M: 0.50 ± 0.02 s; L: 0.54 ± 0.02 s). Subgroup analysis revealed that movement speed was significantly slower for large movements in those patients that performed the task with online visual feedback compared with those without direct visual feedback (repeated-measures ANOVA interaction between MOVEMENT CONDITION and FEEDBACK, $F_{(2)} = 33$; $p < 0.001$, *post hoc* two-sided Student's *t* test: $p = 0.027$, Bonferroni corrected).

### General pattern of movement-related changes in oscillatory activity

Without prior selection of the pallidal recording sites, the time frequency plots averaged across all bipolar recordings in all patients ($n = 22$ patients, 36 hemispheres, total of 104 recording sites) contralateral to the moved side revealed a significant event-related desynchronization (ERD) in the β frequency range (20–30 Hz) starting before movement onset and an α (8–12 Hz) ERD during movement, as well as a broad event-related synchronization (ERS) in the γ frequency band from ~35–105 Hz in all three movement conditions (Fig. 3*A–C*). Also, the β ERD was followed by a rebound synchronization (β ERS) after the end of the movement. Ipsilateral pallidal LFPs showed a similar ERD in the α and β frequency range but a significantly smaller γ band ERS compared with the contralateral side for all three movement

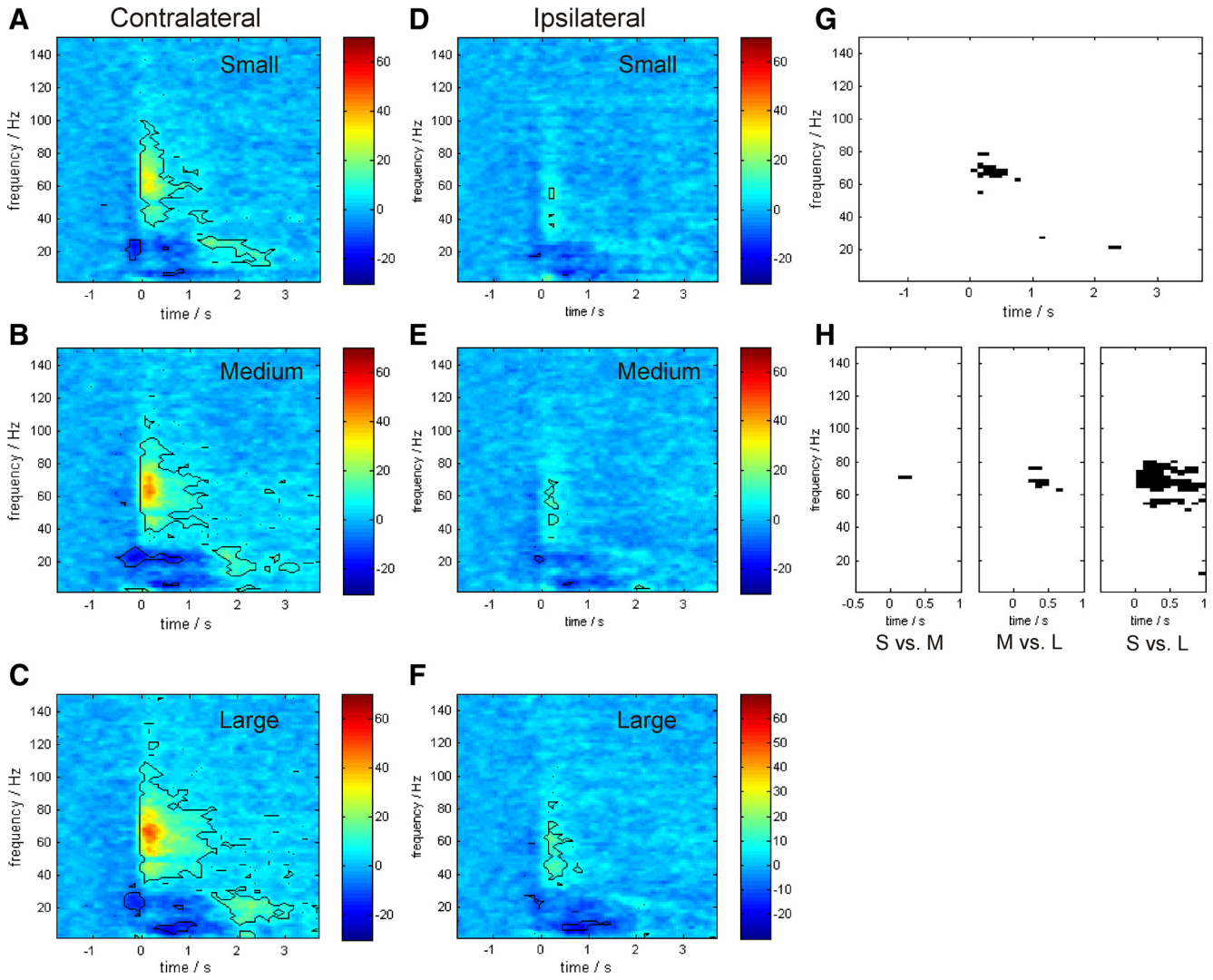


**Figure 3.** ***A–F***, Median oscillatory power changes of 22 patients, 36 contralateral (***A–C***) and ipsilateral (***D–F***) GPi and three contact pairs per electrode ($n = 104$ per side) during small (***A***, ***D***), medium (***B***, ***E***), and large (***C***, ***F***) amplitude movements. Data are expressed as percentage power change compared with baseline (−2 to −1 s before movement onset at time point 0). Contour lines surround bins with $p < 0.01$ (Wilcoxon's signed rank test, FDR corrected). ***G***, Friedman's test of related samples showing bins $p < 0.01$, FDR corrected between movement conditions for contralateral GPi. ***H***, *Post hoc* Wilcoxon's test of oscillatory power changes between movement conditions for contralateral GPi with bins $p < 0.01$, FDR corrected.

conditions (see Fig. 3*D*--*F*). This pattern was similar to previous findings described in pallidal recordings in patients with dystonia (Brücke et al., 2008b) as well as PD patients on levodopa treatment (Androulidakis et al., 2007).

The contralateral γ ERS had a peak reactivity at ~70 Hz and started ~100 ms before movement onset and persisted for up to ~600 ms for the smallest and ~1.5 s for the largest movement. More importantly, the γ ERS showed a parametric modulation with movement amplitudes. Figure 3*G* shows the bins in the time-frequency plot with a significant difference in median oscillatory power between the three movement conditions (Friedman's test of related samples; $p < 0.01$, FDR corrected). The significant bins were restricted to the γ frequency range around the peak reactivity ~ 70 Hz and started ~100 ms after MO. *Post hoc* Wilcoxon's signed rank test confirms the respective differences of median oscillatory power between the three movement conditions focused at ~70 Hz (Fig. 3*H*). No difference in movement-related oscillatory power changes was revealed between the three movement conditions in the lower frequency range (α and β band) or on the ipsilateral side (data not shown). Increases in γ band activity were restricted to movement-related LFP activity. No distinct γ peak was observed in the power spectra from rest recordings.

### Selection of frequency bands and contact pairs

Based on the main findings in the grand average and previous reports, we selected two frequency bands for further analysis that captured the main features of oscillatory power changes during movement. Based on the median matrices, these bands were empirically defined as 20–30 Hz (β band) and 60–80 Hz (γ band). The contact pair per electrode that showed the strongest reactivity in those frequency bands before and during movement was selected for further analysis. We found a well defined maximum of β and γ power changes at one of the contact pairs of the DBS-electrode in all patients, suggesting a locally generated activity. The mean reduction in β ERD at the remaining contact pairs was 44.3 ± 5.9% ($p < 0.05$, two-sided Student's $t$ test). Similarly, the largest γ ERS was 43.7 ± 8.3% higher ($p < 0.001$, two-sided Student's $t$ test) compared with the average of the remaining contact pairs from the same electrode. The correlation of

LFP waveforms between contact pairs revealed a phase reversal in 22 of 36 sides. Electrode placement was verified on postoperative imaging using automated normalization and contact localization in standard MNI stereotactic space coordinates in all patients. In this way we could confirm that all contacts used in our main analysis lay within GPi in all patients (except for case 16 and 22 where image quality of postoperative CT was not sufficient; Fig. 2). Furthermore, in 30 of the 36 selected best contact pairs (83.3%) that showed the highest γ ERS during movement, at least one contact was also used during chronic DBS in our patients, which further supports electrode localization in the motor region of the pallidum.

**Movement-related pallidal activity and movement kinematics**

Time-evolving power changes for the selected frequency bands normalized to baseline activity revealed a significant γ ERS (Fig. 4*A*) and β ERD (Fig. 4*B*). The γ ERS started ~100 ms before movement onset and lasted up to ~1.5 s after movement onset (Fig. 4*A*), although the limited temporal resolution resulting from smoothing has to be considered in our data. Significant departures of the β ERD from baseline started before movement onset and were ongoing during movement. A significant parametric modulation of oscillatory power changes with movement amplitude only occurred in the 60–80 Hz band. Direct comparison of power changes using time-evolving Wilcoxon's signed rank test revealed significant differences between all movement conditions in the 60–80 Hz band (Fig. 4*A*, $p < 0.05$, FDR corrected). Here, the γ ERS was strongest during movements with the largest amplitude and the weakest γ ERS occurred with small movements. In contrast, no significant difference in β ERD occurred with respect to movement amplitude before, during, and up to one second after movement (Fig. 4*B*).

These features were confirmed by repeated-measures ANOVAs with the main factor MOVEMENT CONDITION (3 levels: small, medium, large) for γ band activity averaged in the time-window from MO to 300 ms after MO (Fig. 5*A*). We observed a main effect for movement condition ($F_{(1.2)} = 17.6$; $p < 0.001$; Huynh–Feldt corrected), and *post hoc* Student's *t* test revealed a significant difference between all conditions with a mean γ ERS of 57.6 ± 9% for small, 82.0 ± 12.2% for medium, and 105.7 ± 17.6% for large movements (small vs medium: $p < 0.001$, small vs large: $p < 0.001$, and medium vs large $p = 0.015$, Bonferroni corrected). Whether or not patients had direct online visual feedback during task performance had no effect on the main result as shown by the ANOVA using feedback as between-subject factor ($F_{(1)} = 2.26$; $p = 0.142$). Accordingly, the main results of movement-related increase in γ ERS could be equally shown in both subgroups [$F_{(1.1)} = 12.3$; $p = 0.02$ (Huynh–Feldt corrected) and $F_{(2)} = 11$; $p < 0.001$, respectively]. On an individual level, the movement-related increase in γ ERS was found in 92 of 106 recording sites.

In contrast, for β band activity (Fig. 5*B*), the repeated-measures ANOVA with the main factor MOVEMENT CONDITION (3 levels: small, medium, large) and TIME [2 levels: preMO (−300 ms to MO) vs postMO (MO to 300 ms)] showed no significant effect (MOVEMENT CONDITION: $F_{(2)} = 0.6$; p = 0.52 and TIME: $F_{(1)} = 0.5$; p = 0.48) or interaction ($F_{(2)} = 3$; p = 0.053). Additionally, we conducted a separate ANOVA for β-ERD in the premovement time period that did not reveal a significant effect for condition.

Our main analysis revealed a stepwise increase in event-related power changes with increasing amplitude of the movement that was specific to γ band activity. To further delineate a potential role of pallidal activity in parameterization of movements, we set out to more specifically evaluate oscillatory changes in γ band activity with regard to movement direction, amplitude, and velocity as well as proprioceptive feedback. These analyses were restricted to changes in the 60–80 Hz band based on our general findings.

**Role of movement direction**

In a subgroup of patients ($n = 4$ patients, 5 sides, 14 contact pairs), we tested whether movement-related γ band synchronization was sensitive to movement direction. The mean γ ERS in the time-period from MO to 300 ms after MO was similar for both movements with opposite directions: with initial pronation movements (small 44.7 ± 7.9%, medium 63.8 ± 10.8%, large 84.7 ± 14.1%) and with initial supination movements (small 48.4 ± 10.8%, medium 64.4 ± 16.3%, large 104.3 ± 26.4%; Fig. 6). The repeated-measures ANOVA revealed an effect for MOVEMENT AMPLITUDE ($F_{(1)} = 5.9$, p = 0.019) but no effect of MOVEMENT DIRECTION ($F_{(1)} = 0.15$, p = 0.7) and no interaction between movement amplitude and movement direction ($F_{(1)} = 0.7$, p = 0.4). Additional subgroup analysis restricted to movements with initial supination confirmed a significant effect for MOVEMENT AMPLITUDE (ANOVA $F_{(1)} = 11.3$, $p = 0.004$, Huynh–Feldt corrected). *Post hoc* two-sided Student's *t* test confirmed differences in γ ERS according to movement amplitude regardless of the direction of the movement [small vs medium: $p = 0.09$ (n.s. after Bonferroni correction), small vs large: $p = 0.009$, and medium vs large $p = 0.015$, Bonferroni corrected; data not shown]. With respect to the γ ERS at the selected best contact pair we defined the preferred movement direction for each patient and hemisphere. The γ ERS was consistently larger for the preferred direction at all three contact pairs in all patients (except one hemisphere in one patient that did not show a significant γ synchronization with the supination movement), suggesting that γ synchronization representing population activity from different subregions of the pallidum did not vary with movement direction. Instead, we found a significant correlation between the difference in γ ERS between pronation and supination movement and the difference in the corresponding movement velocity ($r = 0.711$, $p = 0.01$, data not shown).

**Movement onset, velocity, or amplitude**

Behavioral data from our patients revealed a significant increase in movement velocity with increasing amplitude of the movement. To further disentangle the influence of movement velocity and amplitude on γ band ERS, we compared the event-related changes in mean γ band activity averaged over the three movement conditions aligned to three different time-points (set as time point 0): maximum amplitude (maxA), maximum velocity (maxV), and MO (Fig. 7). Interestingly, the maximum of γ band ERS coincided with maxV, suggesting the strongest relationship was between γ power and movement speed. Consistently, the largest γ ERS occurred when γ power was aligned to maxV (Fig. 7). Repeated-measures ANOVA revealed a significant effect for TIME POINT ($F_{(1.3)} = 27.7$; $p < 0.001$ Huynh–Feldt corrected). The mean γ band power increase was 40.03 ± 6.7% for maxA, 73.9 ± 11.2% for maxV, and 54.1 ± 8.5% for MO (each averaged from −200 ms to 200 ms around the respective time-point 0). *Post hoc* Student's *t* test confirmed significant differences between γ ERS during maxA, maxV, and MO ($p < 0.05$, Bonferroni corrected).

Next, we correlated the relative change in γ band synchronization up to 300 ms after MO and 400 ms around maxV with the relative difference in movement speed between all three conditions

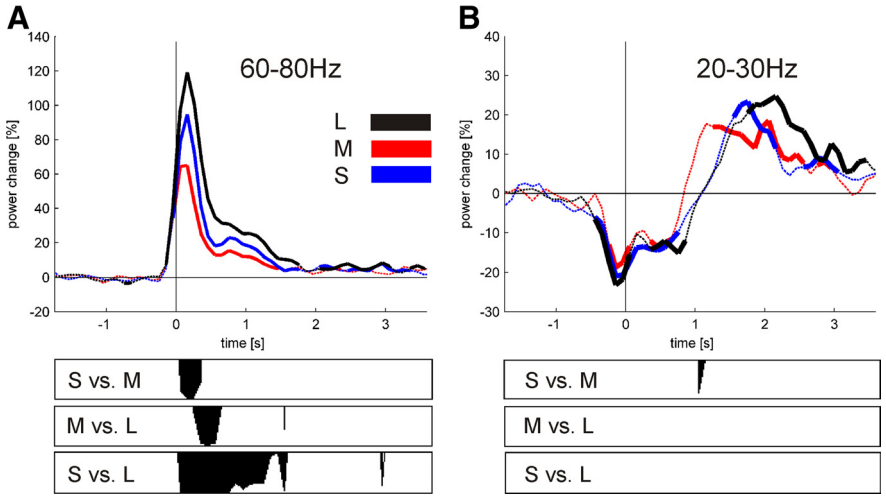


**Figure 4.** ***A***, ***B***, Mean power changes over time for selected contact pairs ($n = 36$) in the γ (***A***; 60–80 Hz) and β (***B***; 20–30 Hz) band expressed as percentage power change compared with baseline −2 to −1 s before MO at time point 0. Note the stepwise increase in γ band activity with larger movement amplitudes (small amplitude— blue line, medium amplitude—red line, large amplitude— black line). Thick lines indicate significant changes ($p < 0.05$, FDR corrected) compared with baseline activity. Lower bars indicate significant differences in Wilcoxon's sign-rank test between movement conditions ($p < 0.05$, FDR corrected) in black.

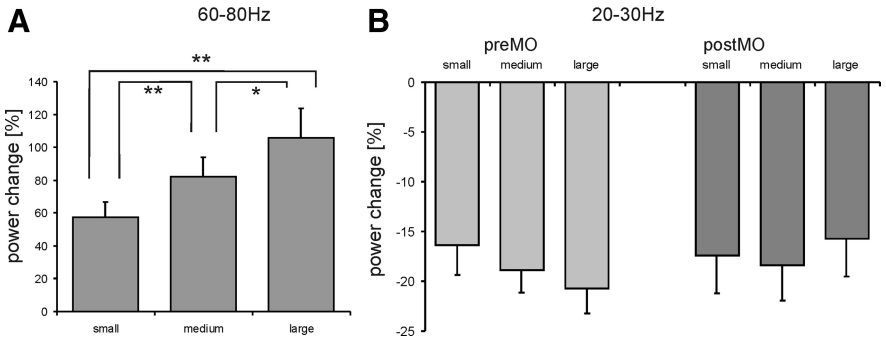


**Figure 5.** ***A***, Mean γ (60–80 Hz) power averaged 0–300 ms after MO for small, medium, and large amplitude movements. ***B***, Mean β power (20–30 Hz) power averaged from −300 ms to MO (preMO) and from MO to 300 ms after MO (postMO) for small, medium, and large amplitude movements. ($n = 36$ electrodes, $^*p < 0.05$, $^{**}p < 0.001$ Student's *t* test, Bonferroni corrected).

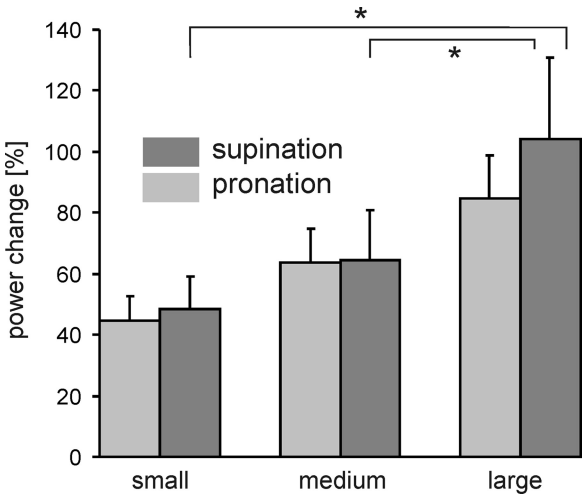


**Figure 6.** Mean γ (60–80 Hz) power averaged 0–300 ms after MO for small, medium, and large amplitude movements during pronation and supination movements. $^*p < 0.05$.

(L-M; L-S; M-S). This revealed a significant positive correlation for both γ ERS at MO ($r = 0.34$, $p < 0.001$) and maxV ($r = 0.351$, $p < 0.001$) with relative movement speed (Spearman's correlation). To further elucidate this relationship, one subject (case 2) was asked to additionally perform externally paced movements with freely chosen angular degree between 1° and 90° with the left forearm leading thus to a higher variability in movement amplitude and velocity on a single trial level. Here, we correlated the γ ERS with movement amplitude and velocity on a single trial level. The 60–80 Hz power in the GPi contralateral to the moved side was averaged >300 ms around maxV and maxA of each trial and correlated with the maximum amplitude and velocity of the corresponding movement, respectively. The highest correlation was seen between the γ response averaged around maxV and movement velocity ($r = 0.45$, $p < 0.001$, Pearson's correlation, Fig. 8). The correlation between movement amplitude and γ ERS averaged around maxA ($r = 0.25$, $p = 0.06$) only showed a trend in this direction. Overall, the amplitude of the movements showed a strong correlation with the movement speed ($r = 0.9$, $p < 0.001$, Pearson's correlation).

### Role of proprioceptive afferent feedback on pallidal γ ERS

Overall, during passive movements a small EMG activation was still present, which was significantly smaller compared with the EMG activity during active movements (Fig. 9*B*). There was no significant difference in mean movement velocity between active and passive movements (paired Student's *t* test, $p = 0.87$). Mean increase in γ band activity averaged across the three movement conditions was significantly stronger during active movement trials compared with passive movements (Fig. 9, mean γ ERS active: 47.8 ± 13.3%; passive: 12.2 ± 6.7%, $p = 0.007$, two-sided Student's *t* test), suggesting that afferent feedback had limited influence on the pallidal γ ERS.

## Discussion

We have shown that γ activity in the GPi LFP contralateral to the moved hand is correlated with movement amplitude and velocity of the hand movement. A stepwise increase in γ band activity was seen with larger and faster hand movements. At lower frequencies (<30 Hz), we observed a symmetrical bilateral decrease that occurred before movement onset and was not modulated by different motor conditions. Thus, the parametric modulation of GPi LFP activity with movement parameters was frequency selective for γ activity and occurred around movement onset, supporting a link between γ oscillations and kinematics of ongoing movements in patients with dystonia with normal hand motor function. The implication is that the GPi as a major output station of the basal ganglia influences, as indexed by the degree of local γ synchronization, the scaling of ongoing movements, whereas a decrease in β band activity might be a more general phenomenon during motor preparation that is necessary to allow movement parameterization through other frequencies (such as γ band activity) to occur (Brown, 2007).

The γ synchronization contralateral to the moved hand is in line with primate studies that have consistently shown

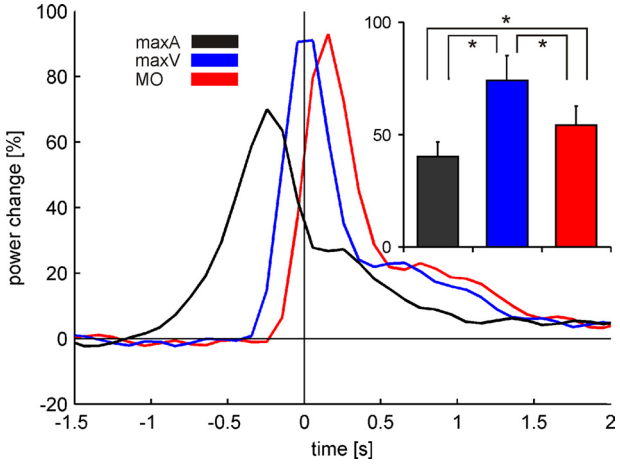


**Figure 7.** Averaged 60–80 Hz power over the three movement conditions (S, M, and L). The LFP epochs were aligned to maxA (black), maxV (blue), and MO (red). The peak of the γ band aligned to the time point of maximum speed at time point 0 hints at strongest relationship between γ power and movement speed. Inset shows mean γ power averaged from −200 ms to 200 ms around time point 0. $*p < 0.05$.

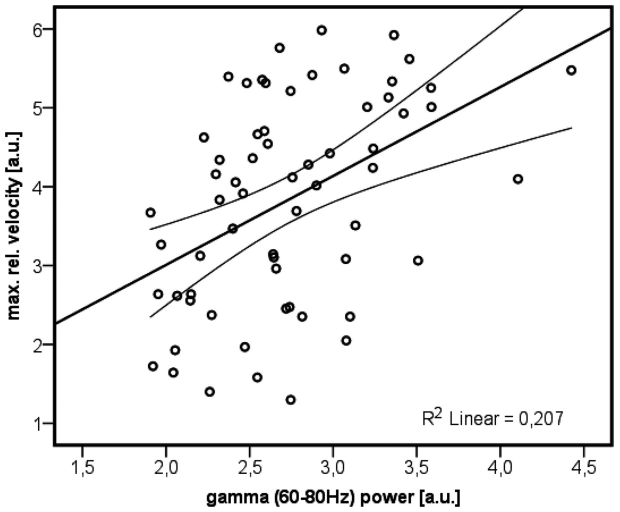


**Figure 8.** Correlation of maximum relative velocity and mean 60–80 Hz power 300 ms around time point maxV on single-trial level from right Gpi in patient 2. Patient performed left arm movements paced by a cue with freely chosen amplitude and velocity.

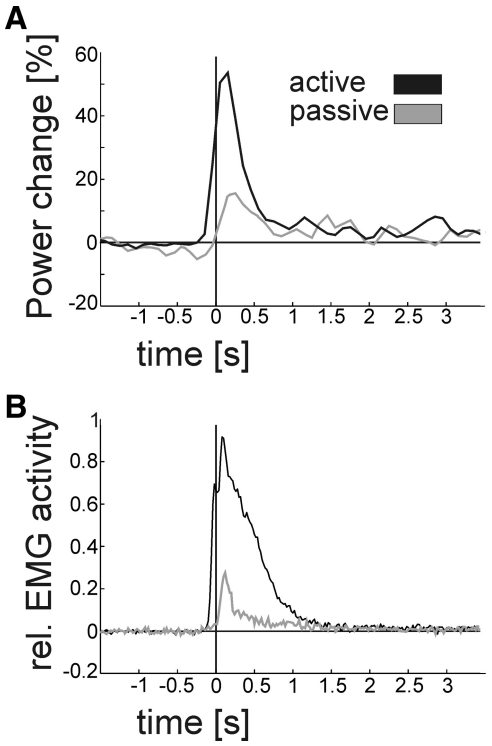


**Figure 9.** ***A***, Averaged 60–80 Hz power during active (black) and passive (gray) movements. Data are from 4 patients and 6 GPi ($n = 6$). ***B***, Averaged relative rectified EMG activity during active and passive movements. Data are averaged across the three movement conditions.

movement-related changes of neuronal discharge rate in the GPi during voluntary movements of the contralateral arm (DeLong, 1971; Georgopoulos et al., 1983; Mink and Thach, 1991a,b). Several studies have found that neuronal discharge rate scales with movement direction, amplitude, and/or speed (Georgopoulos et al., 1983; Turner and Anderson, 1997), but others could not attribute discharge rates to movement kinematics (Mink and Thach, 1991b; Brotchie et al., 1991a; Mushiake and Strick, 1995). Local inhibition with muscimol or kainic acid injection into the primate GPi leads to slowness of movements with prolonged movement time, whereas reaction times do not change (Horak and Anderson, 1984; Mink and Thach, 1991c; Desmurget and Turner, 2008). Perimovement increases in pallidal neuronal firing have been mainly observed at movement onset, i.e., rather late compared with activation of motor cortical areas (Georgopoulos et al., 1983; Mitchell et al., 1987; Jaeger et al., 1995; Turner and Anderson, 1997), suggesting its role in modulation of ongoing tasks and scaling of movements without affecting the initiation and sequential organization of programmed motor output. Moreover, a correlation between BG activity and the velocity or amplitude of the movement was shown in normal subjects using PET (Thobois et al., 2007; Turner et al., 2003) or fMR imaging (Grafton and Tunik, 2011). Prodoehl et al. (2009) proposed that dorsal BG (including the internal pallidum) also regulate the parametrization of grip force, whereas changes in fMRI BOLD signal in the ventral BG scale with the prediction of force amplitude (Vaillancourt et al., 2004, 2007). Based on these observations it has been suggested that basal ganglia output regulates (among other behavioral and sensory dimensions) movement gain (Turner and Desmurget, 2010). In this framework, we would tentatively interpret pallidal γ synchronization that occurred around movement onset in our patients to index BG influence on movement gain. However, it has to be pointed out that other models of BG function have been put forward, suggesting a major contribution of the BG to movement selection and initiation (Mink, 2003; Houk and Wise, 1995; Houk et al., 2007), encoding of context-dependent information of movements, cognitive aspects of motor control (Brotchie et al., 1991b; Mushiake and Strick, 1995; Pasquereau et al., 2007), but also motor learning (Doyon et al., 2009) and feedback control of movements (Brainard, 2004; Brown et al., 2006). Our results showing a parametric modulation of pallidal γ synchronization with increasing velocity of the movement provide support for the scaling hypothesis and related cost functions, and raise the possibility that γ activity may be involved in mediating this scaling. Gamma activity may facilitate information coding and processing (Pogosyan et al., 2006) as well as "motor binding" (Engel et al., 2005), i.e., supporting binding of distributed responses and selection of specific motor parameters. The above does not necessarily imply that γ activity represents explicit motor processing, and γ synchrony may serve

different functions in the visual and motor system. Moreover, increased γ activity has been described in REM sleep without limb movement and following startling stimuli. Both are more likely related to arousal or attentional changes that influence gain leading to greater energization of the movement (Kempf et al., 2009).

A general mechanism by which the basal ganglia may regulate motor control was recently suggested as being the scaling of the effort or motor energy invested in a movement (Mazzoni et al., 2007). In this model of motor control, the effort variable (motor cost) is dependent on the velocity and/or amplitude of movements. Our results would also be in line with the assumption that basal ganglia control motor costs rather than motor parameters, since other kinematic parameters such as movement direction were controlled independently (Vindras et al., 2005) and did not influence the degree of γ synchronization in our patients. However, the present study was not intended to disentangle correlates of motor energy and movement velocity, and future studies should evaluate the potential role of pallidal γ activity for modulation of motor performance according to energetic or other costs to the subject.

In this regard it is interesting to note that motor slowing and reduced amplitude of movements has been observed in patients treated with bilateral high-frequency stimulation of the GPi for Huntington's disease (Moro et al., 2004), dystonia (Ostrem et al., 2007), or Tourette's syndrome (Diederich et al., 2005), possibly induced by interference of high-frequency DBS with physiological pallidal motor output.

There is increasing evidence of movement-related γ band synchronization as a feature of basal ganglia activity that is common across different movement disorders. Gamma band ERS has been recorded from GPi in both generalized and focal dystonia (Brücke et al., 2008; Liu et al., 2008), from the subthalamic nucleus in treated and untreated PD patients, and in patients with nonparkinsonian tremor (Androulidakis et al., 2007; Kempf et al., 2007). The movement-related γ increase was strictly lateralized in patients with dystonia, and lateralization was facilitated by dopaminergic treatment in PD, suggesting a more physiological pattern of motor processing promoted by therapeutic intervention in PD (Androulidakis et al., 2007). Here, our data provide further support to the idea that movement-related lateralized γ band synchronization is a feature of physiological basal ganglia activity encoding information about movement kinematics or energization of movement.

These observations from deep brain recordings are paralleled by activity at the cortical level obtained in ECoG (electrocorticography) in patients with epilepsy (Crone et al., 1998; Crone et al., 2006; Mehring et al., 2004) and in normal subjects using MEG and EEG (Cheyne et al., 2008; Waldert et al., 2008; Ball et al., 2008; Huo et al., 2010) that have demonstrated the occurrence of γ oscillations in a similar frequency range (60–150 Hz) in the primary motor cortex during movement onset contralateral to the moved limb. More recently, Muthukumaraswamy (2010) has revealed that motor cortical γ synchronization is greater with larger movements with a time to peak at ~137 ms after EMG onset, not sustained during isometric contraction, and absent during passive movements. These results are strikingly similar to our observations from deep brain recordings, strongly indicating that γ synchronization at cortical and basal ganglia levels reflects active motor processing at a relatively late stage of motor control. Additionally, the significant correlation of movement velocity and γ synchronization in our data suggests that γ oscillations may encode specific kinematic parameters such as movement velocity or, more general phenomena, such as motor gain and energization of movement. However, whether cortical motor areas drive basal ganglia output at γ frequency or whether movement-related γ synchronization has been generated locally in the GPi cannot be answered since EEG was not available in our patients due to surgical dressings.

We have further shown that pallidal γ synchronization is related to the motor output and is not a result of proprioceptive feedback, since γ increase in pallidal LFP activity during passive movements was significantly smaller compared with active movement. This is in line with results of a previous study using a block design of different sensorimotor conditions that revealed γ synchronization with voluntary but not passive movements in patients with dystonia (Liu et al., 2008).

An important question remains as to how the underlying disease may have influenced our results. We have to bear in mind that results are obtained in patients with movement disorders, thus there is no certainty that findings are physiological. However, to avoid major confounds induced by abnormal hand movements [shown to induce γ activity in generalized dystonia patients, see the study by Liu et al. (2008)], we have only included patients with normal hand motor function in our study. It also has to be noted that abnormal muscle activity has been related to increased low-frequency activity (4–10 Hz) in dystonia patients, and γ band activity is usually not found in the resting state pallidal LFP activity (Liu et al., 2008; Sharott et al., 2008).

In summary, our study provides evidence that basal ganglia output encodes information related to motor gain and that this is at least partly indexed by the degree of pallidal γ band synchronization. This raises the possibility that γ activity may play a role in the communication between neuronal populations during movement execution and regulation of movement gain.

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